Evidence-based Practice Center Systematic Review Protocol

Project Title: Testing of CYP2C19 Variants and Platelet Reactivity for Guiding Antiplatelet Treatment

I. Background and Objectives for the Systematic Review

It is estimated that around 82 million Americans currently suffer from some form of cardiovascular disease (CVD). CVD is the leading cause of death in the United States, with cardiovascular mortality accounting for 34% of all deaths in 2007.[1] Coronary heart disease alone is the cause of 1 of every 6 deaths in the United States; and stroke, 1 of every 18 deaths.[2] In spite of widespread efforts to prevent CVD, it is estimated that every year more than a million Americans have a myocardial infarction and approximately 795,000 Americans experience a first-time or recurrent stroke. The total number of inpatient cardiovascular operations and procedures was approximately 7 million in 2007, of which 1 million were either percutaneous coronary interventions or coronary artery bypass graft surgeries.[1]

Randomized trials have established dual antiplatelet treatment (aspirin and clopidogrel) as the current standard of care for medical and interventional management of acute coronary syndromes, including percutaneous coronary intervention. Randomized trials also support the use of clopidogrel in patients who have experienced acute cardiovascular events (such as stroke), those with peripheral arterial disease, and select patients with atrial fibrillation.[3-6]

The introduction of clopidogrel into routine clinical practice has made it one of the most commonly prescribed drugs in the United States. Despite the proven efficacy of clopidogrel, not all patients appear to respond to the drug. Given the availability of alternative treatments and concern about adverse clinical outcomes in clopidogrel nonresponders, there is a marked interest in developing methods to identify patients who are unlikely to benefit from clopidogrel. Alternatives to standard clopidogrel treatment include higher-dose clopidogrel regimes and use of other antiplatelet agents, such as prasugrel and ticagrelor, that are not metabolized through the same pathways as clopidogrel. Prasugrel and ticagrelor have similar or superior efficacy compared to clopidogrel for preventing major adverse cardiovascular events. However, there is evidence that these drugs may increase the risk of bleeding complications.[7,8]

There are currently two basic approaches for trying to determine whether a patient will have a poor response to clopidogrel: (1) genetic testing to see whether the patient has a genotype that is associated with reduced ability to metabolize clopidogrel, and (2) direct testing of the patient's blood while the patient is taking clopidogrel to see whether the platelets actually have become less prone to aggregate in response to specific agonists (phenotypic testing for platelet reactivity). This creates several dilemmas for clinicians and patients: Which test is most accurate for predicting whether a patient will have a bad outcome on standard clopidogrel therapy? Which test (or combination of tests or no test) provides the best guide for whether a patient should receive standard clopidogrel therapy or whether an alternative treatment strategy should be considered? Does the predictive accuracy of either the genetic or phenotypic test or the effectiveness of test-and-treatment strategies vary according to patient characteristics or comedications?

Genetic and phenotypic tests

Clopidogrel does not possess inherent biological activity; it must be transformed to the active metabolite R-130964 by members of the CYP 450 enzyme system, primarily the enzyme CYP2C19. R-130964 acts by binding irreversibly to the $P2Y_{12}$ receptor (the adenosine diphosphate [ADP] receptor) at the surface of platelets and inhibits platelet aggregation for the duration of the life cycle of the platelet. Platelet aggregation returns to pretreatment levels approximately 5 days after clopidogrel is stopped owing to the production of new (noninhibited) platelets by the hematopoietic system.[9-12]

The CYP2C19 gene is highly polymorphic, with more than 35 identified variants. Following the recommendations of the Human Cytochrome P450 Allele Nomenclature Committee,[a] each of these variants is designated by a number (e.g., "*1", "*2"). Genetic variants of the CYP2C19 locus can affect the encoded protein: some lead to normal enzymatic activity (denoted as CYP2C19*1 alleles, corresponding to a normal metabolizer phenotype), while others lead to complete elimination of enzymatic activity (e.g., CYP2C19*2, *3, and *4, all loss-of-function alleles corresponding to a nonmetabolizer phenotype), and still others lead to increased enzymatic activity (e.g., CYP2C19*17, corresponding to an ultrametabolizer phenotype).[13] Each individual carries two CYP2C19 alleles, which results in combinations of alleles of varying enzymatic activity and leads to additional variation in the observed metabolic phenotypes. For example, carriers of a *1/*2 genotype have an intermediate metabolizer phenotype between *1/*1 (normal metabolizer) and *2/*2 (nonmetabolizer).

A genome-wide association study recently demonstrated that CYP2C19*2 is the main genetic determinant of variability in clopidogrel responsiveness and accounts for 12 percent of the total observed variation in this trait.[14] Experimental studies of healthy volunteers, as well as studies of patients with CVD, have consistently shown that CYP2C19 genotypes can be used to predict the phenotype of on-clopidogrel platelet reactivity. Such studies have also suggested that alternative treatment strategies (e.g., higher clopidogrel dosing or use of prasugrel or ticagrelor) can overcome the effects of genotype on platelet reactivity.[15-17]

Phenotypic testing measures the reactivity of platelets while a patient is taking clopidogrel. Several assays for measuring platelet reactivity are available. These include rapid (point-of-care) platelet function assays (e.g., VerifyNow, PFA-100, Plateletworks), measurements of mediators of reactivity (e.g., vasodilator-stimulated phosphoprotein phosphorylation using flow cytometry), and functional assays (e.g., turbidimetric, impedance, and conductance aggregometry using appropriate agonists). We refer to all these assays as "phenotypic tests," because they attempt to measure an intermediate clinical phenotype (platelet reactivity). There is no universal gold standard for the evaluation of platelet aggregation, and the performance of available tests is not standardized.[18] Studies using such assays have demonstrated that platelet response to clopidogrel is variable (both between patients and over multiple measurements on the same patient), with some patients showing no platelet response to clopidogrel administration (often termed clopidogrel "nonresponsiveness" or "resistance").

Use of genetic and phenotypic tests to predict patient outcomes

Five systematic reviews that included quantitative analyses (meta-analyses, published in 2010–2011) have assessed the utility of CYP2C19 variants for predicting major clinical outcomes in patients receiving clopidogrel.[19-23] All the reviews found statistically significant associations between

[a] Available at: http://www.cypalleles.ki.se/; last accessed September 19, 2011.

reduced-activity CYP2C19 alleles and major adverse cardiovascular events; however they reached contradictory conclusions. One of the reviews found evidence of "publication bias" and concluded that the evidence "does not indicate a substantial or consistent influence of CYP2C19 gene polymorphisms on the clinical efficacy of clopidogrel"; however, all other reviews reached favorable conclusions regarding the use of CYP2C19 genetic testing for response prediction.

Four additional meta-analyses have assessed the predictive utility of phenotypic tests for platelet reactivity.[24-27] All four supported the existence of a significant association between clopidogrel nonresponsiveness (i.e., high on-clopidogrel platelet reactivity, as determined by laboratory tests of platelet reactivity) and adverse cardiovascular outcomes. In meta-analyses of both phenotypic and genetic tests, the summary effect sizes were low or moderate for most outcomes. Low effect sizes indicate that the discriminatory ability of the tests may be low, leading to uncertainty about the clinical utility of testing. In addition, all existing meta-analyses of CYP2C19 variants have only considered studies that enrolled patients from predominantly white populations, resulting in considerable uncertainty about the utility of the tests for individuals of other racial or ethnic backgrounds. Furthermore, existing reviews have not assessed comparative test performance for predicting outcomes.

Our preliminary searches indicate that an updated systematic review would address these issues by attaining higher statistical power (owing to the increased number of available studies), by including studies of patients of nonwhite racial or ethnic groups (which have been published since the completion of prior reviews) and considering studies directly comparing test performance.

Use of genetic and phenotypic tests to guide antiplatelet therapy

While clinicians and patients may find it helpful to know the probability of good or bad outcomes, predictive tests are most valuable when they inform treatment decisions. The observation that specific CYP2C19 variants or levels of on-treatment platelet reactivity above a threshold predict worse outcomes does not necessarily mean that changing treatment on the basis of these tests will improve outcomes. It is possible that the genotype or phenotype is simply a marker for poor outcomes regardless of treatment strategy used. Therefore the evidence of test impact on treatment decisions and subsequent patient outcomes must be considered separately from outcome prediction. Randomized trials of testing strategies versus no-testing strategies can address the question of whether the use of testing (e.g., genetic testing to determine CYP2C19 status or phenotypic testing of platelet reactivity) affects clinical outcomes.[28] When such comparative studies are not available, evidence can be obtained by repurposing completed randomized controlled trials for which baseline samples are available to perform genetic analyses. In such cases, one can analyze all the samples (e.g., samples from the clopidogrel group and from the comparator or control group) for the genetic marker of interest (here, CYP2C19 polymorphisms) and then assess the interaction of the biomarker status with the treatment effect.[29,30] However, recently published studies have failed to identify an interaction between genetic test results and treatment outcomes.[31,32] Absence of such interactions indicates that the utility of genetic testing for guiding treatment decisions may be limited; however, even large trials may have inadequate power to detect heterogeneity of treatment effects. A synthesis of the relevant existing evidence, with a focus on interaction effects, may increase the statistical power to detect effect modification.

Modifiers of the predictive value and clinical utility of tests

Proton-pump inhibitors (PPIs) are often prescribed along with antiplatelet therapy to limit the potential for gastrointestinal bleeding complications. Because CYP2C19 is the key enzyme in the

metabolism of several PPIs, it has been hypothesized that coadministration of these drugs could inhibit the activation of clopidogrel.[33] A recent systematic review that examined studies investigating the association between PPI use and adverse cardiovascular events among patients receiving clopidogrel concluded that PPI use was associated with an approximately 40 percent increase in the risk of major adverse cardiovascular outcomes and an 18 percent increase in mortality.[19] However, no systematic review has assessed the interaction of PPIs with the clopidogrel treatment effect within categories defined by CYP2C19 status or platelet reactivity. Other potential modifiers of the utility of genetic and phenotypic test results include the specific indication for clopidogrel use (because the predictive ability of testing may vary between patient populations), race or ethnicity (because of the varying prevalence of CYP2C19 alleles among different ethnic groups), comorbid conditions (that may affect the baseline event rate or serve as markers for the coadministration of drugs metabolized by CYP2C19), baseline disease severity, sex, and age.

Summary

In summary, there are areas of uncertainty regarding the use of both genetic tests for CYP2C19 variants and phenotypic tests for platelet reactivity. There is controversy regarding the value of these tests for predicting clinical outcomes (e.g., mortality, myocardial infarction, or other cardiovascular events) in patients who are receiving clopidogrel. There is also insufficient information about whether the results of these tests can be used to guide therapeutic decisionmaking for antiplatelet therapy. Assessments of comparative effectiveness should consider both the benefits and harms (due to testing and test-directed treatment) associated with each strategy. The modifiers of these tests' effects, both in terms of predictive ability and therapeutic decisionmaking, also need to be clarified. To review the available evidence addressing the issues outlined above, we will perform a systematic literature review regarding the utility of testing for CYP2C19 variants and platelet reactivity for guiding antiplatelet treatment.

II. The Key Questions

On the basis of comments received from public review and input from local experts, we have revised the Key Questions and study eligibility criteria to clarify the focus of the current comparative effectiveness review (CER). These questions broadly follow the ACCE framework, covering Analytic validity, Clinical validity, Clinical utility, and test-related harms.

The following four Key Questions will be addressed in the current CER:

Key Question 1

In patient populations who are candidates for clopidogrel therapy, does genetic testing for CYP2C19 variants predict intermediate and clinical outcomes following treatment initiation?

a. What is the analytic validity (technical test performance) of the various assays used for CYP2C19 genetic testing?
b. What is the clinical validity (predictive accuracy) of genetic testing for predicting intermediate and clinical outcomes in patients who are receiving clopidogrel therapy?
c. Do the following factors modify the association between genetic test results and clinical outcomes?
    i. Comedications
    ii. Patient-level factors (e.g., race or ethnicity, age, sex, disease severity, or comorbidities)
    iii. Test-related factors (e.g., between-assay differences)
    iv. System-level factors (e.g., settings where testing is performed)

Key Question 2

In patient populations receiving clopidogrel therapy, does phenotypic testing of platelet reactivity predict intermediate and clinical outcomes?

a. What is the analytic validity (technical test performance) of the various assays used in phenotypic testing of platelet reactivity?
b. What is the clinical validity (predictive accuracy) of phenotypic testing for predicting intermediate and clinical outcomes in patients who are receiving clopidogrel therapy?
c. Do the following factors modify the association between phenotypic test results and clinical outcomes?
    i. Comedications
    ii. Patient-level factors (e.g., race or ethnicity, age, sex, disease severity, or comorbidities)
    iii. Test-related factors (e.g., between-assay differences)
    iv. System-level factors (e.g., settings where testing is performed)

Key Question 3

What is the comparative effectiveness of alternative test-and-treat strategies (including a no-testing strategy) for therapeutic decisionmaking regarding antiplatelet therapy among patients who are candidates for clopidogrel-based treatment?

a. What is the comparative effectiveness of the following testing strategies on therapeutic decisionmaking, platelet reactivity during followup, and clinical outcomes in patients who are candidates for antiplatelet treatment?
   i. Genetic testing for CYP2C19
   ii. Genetic testing for CYP2C19 followed by phenotypic testing for platelet reactivity
   iii. Phenotypic testing for platelet reactivity
   iv. No testing
b. How do modifying factors (e.g., race or ethnicity, age, sex, comorbidities, diet, or the time between conducting the test and obtaining results) affect the association of alternative phenotypic or genetic test-and-treat strategies and patient outcomes? Alternative test-guided treatments can include nonclopidogrel antiplatelet agents or high-dose clopidogrel regimens.

Key Question 4

What are the potential adverse effects or harms from genetic or phenotypic testing *per se* or from test-directed treatments?

Eligibility criteria

- **Populations—for all Key Questions**

  Adult patients with cardiovascular, cerebrovascular, or peripheral arterial disease who are candidates for or are receiving clopidogrel treatment, including:
  - Patients with acute coronary syndromes, including those who have experienced a myocardial infarction (ST-elevation or non–ST-elevation), or patients who have unstable angina
  - Patients undergoing percutaneous coronary intervention for acute coronary syndromes, those who have undergone percutaneous coronary intervention with stent implantation (of either bare-metal or drug-eluting stents), or those who have undergone coronary artery bypass grafting surgery (and have a contraindication to acetylsalicylic acid)
  - Patients with a previous ischemic stroke or transient ischemic attack
  - Patients with established peripheral arterial disease
  - Patients with atrial fibrillation for whom vitamin K antagonist therapy is not suitable

Relevant studies will be organized in appropriate subgroups on the basis of the clinical indications for clopidogrel use (e.g., separate subgroups re acute coronary syndromes, stroke, and atrial fibrillation not suitable for vitamin K antagonists). Subgroups of interest for assessing effect modification will be those defined by race or ethnicity, sex, specific assay used, and clinical

setting of test use (e.g., acute cardiac events or percutaneous coronary intervention vs. chronic clopidogrel use).

- **Interventions**

  - For Key Questions 1 and 2 (predictive effects) and 4: use of genetic testing (for CYP2C19 variants) or phenotypic testing in patients who are receiving clopidogrel-based antiplatelet therapy. Genetic variants of interest will be all variants of the CYP2C19 locus, including loss- and gain-of-function alleles. Phenotypic tests of interest will be those assessing reactivity (the degree to which platelets are able to be activated by an agonist). Tests of platelet activation will not be considered as they are not in wide clinical use and are less standardized than tests of reactivity.
  - For Key Questions 3 (comparative effectiveness of test-and-treat strategies) and 4: management strategies involving genetic testing for CYP2C19 variants or phenotypic testing for platelet reactivity, followed by therapeutic management decisions based on test results. Potential test-and-treat strategies will include testing for CYP2C19 genetic variants, testing for platelet reactivity, or both, to guide choosing among alternative antiplatelet treatment strategies (including standard clopidogrel dosing, increased clopidogrel dosing, and non–clopidogrel-based antiplatelet therapies such as ticagrelor or prasugrel).

- **Comparators**

  - For Key Questions 1 and 2 (predictive effects):
    - No use of genetic testing (for CYP2C19 variants) or phenotypic testing (for platelet reactivity).
    - Studies comparing the predictive accuracy of more than one genetic or phenotypic test in the same patient population will also be considered.

  - For Key Question 3 (comparative effectiveness of test-and-treat strategies):
    - A no-testing strategy or alternative test-and-treat strategies (as listed under "Interventions" for KQ 3).

- **Outcomes**

  - For Key Questions 1a and 2a (analytic validity):
    - Analytic accuracy (analytic sensitivity and specificity)
    - Analytic precision
    - Test detection limits
    - Dilution linearity
    - Test-retest reliability (e.g., intra-assay agreement, measurement reproducibility)
    - Inter-assay agreement
    - Inter-laboratory comparisons (e.g., inter-laboratory agreement, measurement reproducibility)

- Proportion of nonevaluable samples

- For Key Questions 1b, 1c, 2b, and 2c:
  - Intermediate outcomes
    - Platelet reactivity (when it is used to assess treatment effects)
  - Predictive accuracy for clinical events
    - Overall mortality
    - Myocardial infarction (fatal or non-fatal)
    - Ischemic stroke (fatal or non-fatal)
    - Cardiovascular death
    - Stent thrombosis (for patients with implanted stents)
    - Combinations of the above (composite clinical outcomes)
    - Bleeding events (categorized by severity and by the organ system affected)
    - Health-related and overall quality of life

- For Key Question 3:
  - Intermediate outcomes
    - Platelet reactivity (when it is used to assess treatment effects)
    - Impact on therapeutic decisionmaking (change in clinical decisions based on test results)
  - Clinical outcomes
    - Overall mortality
    - Myocardial infarction (fatal or nonfatal)
    - Ischemic stroke (fatal or nonfatal)
    - Cardiovascular death
    - Stent thrombosis (for patients with implanted stents)
    - Combinations of the above (composite clinical outcomes)
    - Bleeding events (categorized by severity and by the organ system affected)
    - Health-related and overall quality of life

- For Key Question 4
    - Adverse effects of test-directed treatment (including bleeding events and other adverse events such as gastrointestinal events and liver toxicity)
    - Adverse effects of testing per se (including test-related anxiety and adverse events secondary to venipuncture).

- **Timing— for all Key Questions**

  We plan to consider short-term and long-term outcomes separately (using a cut-off time of 30 days, wherever appropriate). For patients undergoing invasive or interventional procedures (e.g., percutaneous coronary intervention or coronary artery bypass grafting surgery), we intend to consider periprocedural events separately.

- **Settings—for all Key Questions**

All relevant care settings (e.g., primary and secondary care). Study selection will not be based on cointerventions.

- **Study designs—for all Key Questions**
    - Studies of analytic validity (for single laboratory studies or inter-laboratory comparisons)
    - Observational studies using the tests of interest to predict outcomes, including studies comparing the predictive ability of more than one test.
    - Randomized controlled trials of test-and-treat strategies
    - Nonrandomized comparative studies of test-and-treat strategies

III. Analytic Framework

Figure 1. Analytic framework for Testing of CYP2C19 Variants and Platelet Reactivity for Guiding Antiplatelet Treatment

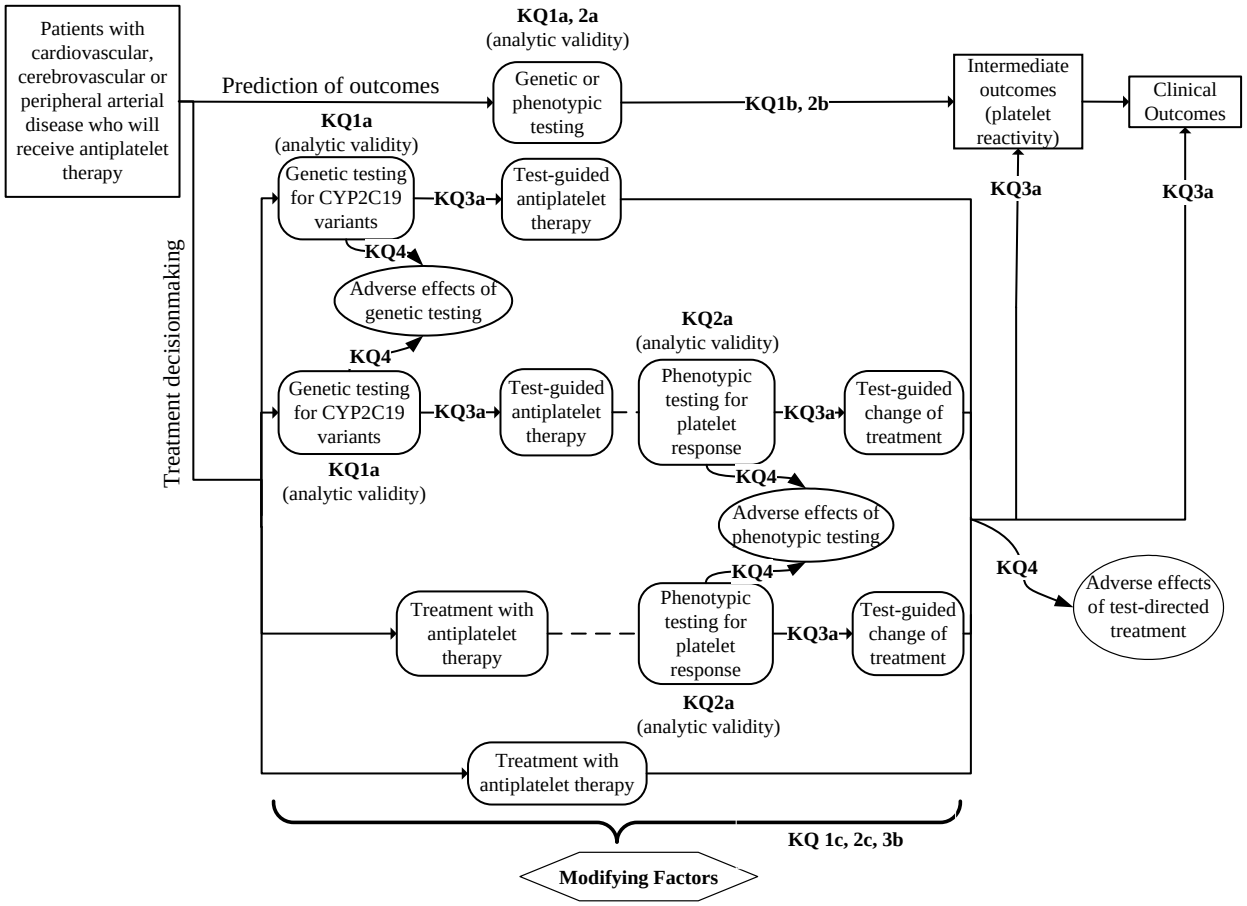

Figure 1. The Key Questions are shown within the context of the PICO (Population, Intervention, Comparators, and Outcomes) criteria. The figure illustrates that results of genetic tests for CYP2C19 or of phenotypic tests of platelet reactivity in patients with heart disease who are receiving, or are candidates for, clopidogrel therapy may affect the prediction of outcomes and treatment. The diagnostic accuracy of each test will also be addressed.

For patients for whom a treatment decision has been made (or is dictated by concerns such as availability of the drug in a specific setting or known history of toxicity), the tests (both phenotypic and genetic) may still be useful for predicting clinical outcomes. The predictive ability of each test is addressed in Key Questions 1b, 1c, 2b, and 2c. Perhaps more importantly, the test results can influence treatment decisionmaking (i.e., be part of test-and-treat strategies) and thereby affect the incidence of major clinical outcomes (the comparative effectiveness of each strategy is addressed by Key Questions 3a and 3b). Tests and test-directed treatments may be associated with harms (Key Question 4). Modifiers of the testing effect on clinical outcomes

(both in terms of predictive ability and decisionmaking) are addressed by Key Questions 1c, 2c, and 3c. The analytic validity of phenotypic tests will be considered in Key Questions 1a and 2a.

Regarding treatment decisionmaking, we conceptualize the analytic framework as a decision problem. Patients can be managed with one of the following approaches (from top to bottom in the graph):

1. Undergo genetic testing and then base the treatment decision on the test results.
2. Undergo genetic testing and then base the treatment decision on the test results. After receiving therapy for an adequate period of time, undergo phenotypic testing for platelet reactivity and use the results to decide whether the treatment strategy should be modified.
3. Receive standard treatment directly and, after an appropriate amount of time, undergo phenotypic testing for platelet reactivity and use the test results to decide whether the treatment strategy should be modified. Use of phenotypic testing (but not genetic testing) as a monitoring test can be considered as a variation of this strategy. After a particular treatment is assigned, the test can be performed repeatedly with the aim of adjusting the therapeutic strategy (if the treatment response is deemed to be inadequate). This approach represents a special case of modifying the treatment regimen on the basis of reactivity measurements taken after treatment initiation, the only difference being that the test is performed repeatedly during followup with the aim of modifying treatment if reactivity is found to be above a predefined threshold.
4. Receive antiplatelet therapy without undergoing any testing.

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

We will use the eligibility criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs and setting (PICOTS) as described for the Key Questions pertaining to the genetic and phenotypic tests of interest (Section II above). Here, we provide some additional details about the inclusion and exclusion criteria we plan to use for each Key Question.

Key Questions 1a and 2a (analytic validity):

- Single- or multiple-laboratory studies reporting on metrics of analytic validity (listed under "Outcomes" above)
- N>50. The precision of estimates of analytic validity depends on the specific statistic used; generally, a sample size of 50 excludes studies that are too small to be informative without being otherwise restrictive

Key Questions 1b and 2b (predictive ability):

- Prospective or retrospective cohort studies
- Arms of randomized controlled trials or nonrandomized comparative studies on which tests of interest were used
- Case–control studies (only for Key Question 1b)
- N>10 subjects (per arm, if there are ≥2 arms); smaller sample sizes are unlikely to provide estimates of predictive effects that are adequately precise
- Studies that report or allow for the calculation of sensitivity or specificity, relative risk metrics, or other measurements of classification performance for the tests of interest

Key Questions 1c and 2c (modifiers of predictive ability):

- Prospective or retrospective cohort studies
- Arms of randomized controlled trials or nonrandomized comparative studies on which tests of interest were used
- Case–control studies
- N>10 subjects (per arm, if there are ≥2 arms); smaller sample sizes are unlikely to provide estimates of effect modification that are adequately precise

Key Question 3 (comparative effectiveness of test-and-treat strategies):

- Randomized controlled trials
- Nonrandomized comparative studies
- N>10 subjects (per arm, if there are ≥2 arms); smaller sample sizes are unlikely to estimate comparative effectiveness with adequate precision
- Studies that report or allow for the calculation of relative risk metrics for clinical outcomes, measurements of platelet reactivity or quality of life during followup, or comparing alternative test-and-treat strategies

Key Question 4:

- Prospective or retrospective cohort studies
- Randomized controlled trials

- Nonrandomized comparative studies
- Prospective or retrospective cohort studies
- Case–control studies
- N>10 subjects (per arm, if there are ≥2 arms)

Additional criteria:

- For Key Questions 1b, 1c, 2b, 2c, 3, and 4, we will exclude studies exclusively reporting on healthy individuals.
- For all Key Questions, we will exclude editorials, commentaries, narrative reviews, letters to the editor, and other manuscripts not reporting primary research findings.
- For Key Questions pertaining to effect modification (Key Questions 1c, 2c, and 3c) we will require that studies report formal interaction tests or allow for the calculation of statistics that compare the test effect among strata of the modifier of interest. For example, for studies reporting modification of the CYP2C19 effect by PPIs, we will require the reporting of treatment effect metrics stratified by PPI use as well as CYP2C19 status.

B. Searching for Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Appendix 1 describes our proposed literature search strategy. This search will be conducted in MEDLINE® and the Cochrane Central Register of Controlled Trials. We will also use two annotated databases of studies on genetic associations, the Human Genome Epidemiology Network (HuGe Net) Literature Finder[b] and the National Institutes of Health Genetic Association Database,[c] to identify additional studies of CYP2C19 variants. We will not use any language restriction in our search strategy.

A common set of 400 abstracts will be screened by all reviewers and discrepancies will be discussed in order to standardize screening practices and ensure understanding of screening criteria by all team members. The remaining citations will be split into nonoverlapping sets, each screened by a single reviewer. Abstracts considered not relevant by a reviewer will be reviewed by a second team member to increase the sensitivity of the screening process.

Potentially eligible citations (i.e., abstracts considered potentially relevant by at least one reviewer) will be obtained in full text and reviewed for eligibility on the basis of the predefined inclusion criteria. Full-text articles will be screened independently by two reviewers for eligibility. Disagreements regarding article eligibility will be resolved by consensus involving a third reviewer. We will include only English-language studies during full text review because our preliminary searches indicate that non–English-language studies are few and have small sample sizes; as such, they are unlikely to affect our conclusions. We will generate a list of reasons for exclusion for all studies excluded after full text screening.

We will ask technical experts to provide citations of potentially relevant articles. Additional studies will be identified through the perusal of reference lists of eligible

[b] Available at http://www.hugenavigator.net/HuGENavigator/startPagePubLit.do; last accessed September 19, 2011.
[c] Available at http://geneticassociationdb.nih.gov/; last accessed September 19, 2011.

studies, published clinical practice guidelines, relevant narrative and systematic reviews, conference proceedings, Scientific Information Packages from manufacturers, and a search of U.S. Food and Drug Administration databases. All articles identified through these sources will be screened for eligibility against the same criteria as for articles identified through literature searches. If necessary, we will revise the search string so that it can better identify articles similar to those missed by our current search strategy.

Following submission of the draft report, an updated literature search (using the same search strategy) will be conducted. Abstract and full-text screening will be performed as described above. Any additional studies that meet the eligibility criteria will be added to the final report.

C. Data Abstraction and Data Management

Data will be extracted into standard forms. The basic elements and design of these forms will be the similar to those we have used for other CERs and will include elements that address population characteristics, sample size, study design, descriptions of the test and reference standard, analytic details, and outcomes. Prior to extraction, forms will be customized to capture all elements relevant to the Key Questions. We will use separate forms for Key Questions related to predictive test performance, factors affecting (modifying) predictive test performance, and the effectiveness of test-and-treatment strategies. We will test the forms on several studies extracted by all team members to ensure consistency in operational definitions. If necessary, forms will be revised before full data extraction. We will also consult with the Technical Expert Panel to ensure that all items of clinical or research importance are captured.

Data from each eligible study will be extracted by a single reviewer. The extraction will be reviewed and confirmed by at least one more team member (for data verification). Disagreements will be resolved by consensus including a third reviewer.

D. Assessment of Methodological Quality of Individual Studies

We will assess the methodological quality, or risk of bias, for each individual study using the assessment instrument detailed by the Agency for Healthcare Research and Quality in its *Methods Guide for Effectiveness and Comparative Effectiveness Review,s*[34,35] hereafter referred to as the Methods Guide. For studies of analytic validity, we will base our assessment on items from the checklist recently proposed by Sun 2011.[36] For studies of predictive accuracy, we will use items from the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) checklist.[37,38] For intervention studies (e.g., studies of testing versus no testing), we will use items from the Cochrane risk of bias tool.[39] We will not merge items into "composite" quality scores. Instead, we will assess and report each methodological quality item (as Yes, No, or Unclear/Not Reported) for each eligible study. We will rate each study as being of high, medium, or low risk of bias (quality C, B, or A, respectively) on the basis of adherence to accepted methodological principles. "Quality A" studies have the least likelihood of bias. These studies generally have the following features: lowest likelihood of confounding due to comparison to a randomized controlled group, a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; clear reporting of dropouts and a

dropout rate less than 20 percent; and no apparent bias. "Quality B" studies are susceptible to some bias, but not sufficiently to invalidate results. They do not meet all the criteria in category A owing to some deficiencies, but none are likely to introduce major bias. Quality B studies may not be randomized or may be missing information, making it difficult to assess limitations and potential problems. "Quality C" studies are those considered to carry a substantial risk of bias that may invalidate the reported findings. These studies have serious errors in design, analysis, or reporting and contain discrepancies in reporting or have large amounts of missing information.

If quantitative analyses are undertaken, we will consider performing subgroup analyses to assess the impact of each quality item on the meta-analysis results. The grading will be outcome specific, such that a given study that reports its primary outcome well but did an incomplete analysis of a secondary outcome would be graded of different quality for the two outcomes. Studies of different designs will be graded within the context of their study design. Thus randomized controlled trials will be graded as having a high, medium, or low risk of bias, and observational studies will be separately graded as having a high, medium, or low risk of bias.

E. Data Synthesis

We will summarize included studies qualitatively and present important features of the study populations, designs, interventions, outcomes, and results in summary tables. Population characteristics of interest include age, sex, race/ethnicity, indications for clopidogrel use, patient comorbidities. Design characteristics include methods of population selection and sampling and followup duration. Intervention characteristics include cut-offs used in index and reference tests, technical characteristics of the assays used, frequency of measurements, and details of the test-and-treat algorithms used (when applicable). Outcomes include platelet reactivity and quality of life (measured during followup), changes in therapeutic decisionmaking, mortality, and morbidity. Results include metrics of analytic validity (e.g., sensitivity, specificity, measures of variability), metrics of predictive ability (sensitivity, specificity, relative risk metrics comparing outcomes stratified by test results, and other measures of [re-]classification performance[40]) and relative-risk metrics (e.g., odds ratios or hazard ratios comparing outcomes stratified by test-and-treat strategy, for comparative studies of test-and-treat strategies) or platelet reactivity and quality of life measurements (during followup, for comparative studies of test-and-treat strategies).

We will judge whether the eligible studies are sufficiently similar to be combined in a meta-analysis on the basis of clinical heterogeneity of patient populations and interventions and testing strategies, as well as methodological heterogeneity of study designs and outcomes reported. The determination on the appropriateness of meta-analysis will be made before any data analysis; we will not base the decision to perform meta-analysis on statistical criteria for heterogeneity. Such criteria are often inadequate (e.g., low power when the number of studies is small) and do not account for the ability to explore and explain heterogeneity by examining study-level characteristics. Meta-analysis of predictive accuracy, including meta-analyses of predictive sensitivity and specificity or meta-analyses of relative risk metrics (odds ratios, risk rations, hazard ratios) for clinical outcomes, will be undertaken when there are more than three unique

studies that used the same test (genetic or phenotypic) and reported the same outcomes. Additional meta-analyses may be performed for studies using continuous outcomes to compare groups defined by test results (e.g., studies comparing treatments stratified by genetic test results and using platelet reactivity as a biomarker of outcome). Appropriate methods will be used to account for crossover trial designs.[41] If performed, all meta-analyses will be based on random effects models. Sensitivity analyses (including leave-one-out analyses, analyses assuming a fixed effects model, and reanalyses after excluding a group of studies or the first study on a specific exposure–outcome association) may be undertaken if considered appropriate (e.g., in the presence of studies with outlying effect sizes or evidence of temporal changes in effect sizes).

Differences in the effect sizes for each outcome of interest between more precise (larger) and less precise (smaller) studies will be assessed using the Egger regression-based test for small-study effects.[42] This test is often referred to as a test for publication bias; however, reasons other than publication bias can lead to a statistically significant result, including "true" heterogeneity between smaller and larger studies, other biases, and chance.[43-45]

For all statistical tests, except those for heterogeneity, statistical significance will be defined as two-sided $p < 0.05$. Heterogeneity will be considered statistically significant when the p-value of the Q statistic is $P < 0.1$, to account for the low statistical power of the test.[46]

F. Grading the Evidence for Each Key Question

We will follow the Methods Guide to evaluate the strength of the body of evidence for each Key Question with respect to four domains: risk of bias, consistency, directness, and precision.[34,35] Briefly, we will define the risk of bias (low, medium, or high) on the basis of the study design and the methodological quality of the studies.

We will rate the consistency of the data as *no inconsistency*, *inconsistency present*, or *not applicable* (if there is only one study available). We do not plan to use rigid counts of studies as standards of evaluation (e.g., four of five studies agree, therefore the data are consistent); instead, we will assess the direction, magnitude, and statistical significance of all studies and make a determination. We will describe our logic where studies are not unanimous.

We will assess directness of the evidence ("direct" vs. "indirect") on the basis of the use of surrogate outcomes (e.g., platelet reactivity vs. clinical events as the outcomes of interest) or the need for indirect comparisons (e.g. when tests have not been directly compared in terms of predictive ability or utility for treatment decisionmaking and inference is based on observations across studies).

We will assess the precision of the evidence as precise or imprecise on the basis of the degree of certainty surrounding each effect estimate. A precise estimate is one that allows for a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g., both clinically important superiority and inferiority—a situation in which the direction of effect is unknown) and that therefore precludes a conclusion.

Finally, we will rate the body of evidence on the basis of four strength of evidence levels: high, moderate, low, and insufficient.[34,35] These will describe our level of

confidence that the evidence reflects the true effect for the major comparisons of interest.

G. Assessing Applicability

We will follow the Methods Guide to evaluate the applicability of included studies to patient populations of interest.[34,35] We will evaluate studies (or subgroups of studies) of elderly adults (operationally defined as patients 65 years of age or older) separately if data are available. Applicability will also be judged separately for various indications of clopidogrel use (e.g., chronic treatment of atrial fibrillation versus use for acute coronary syndromes or after percutaneous coronary intervention), patient sex (men vs. women) and race or ethnicity (because CYP2C19 variants have different prevalence according to race/ethnicity).

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VI. Definitions of Terms

Analytic validity: Analytic validity refers to the technical performance of a test—that is, how well does the test measure what it is designed to measure? Specific components of analytic validity are accuracy (sensitivity and specificity), reliability across repeat testing, and agreement in results within and across patients. Analytic validity can be affected not only by the technical characteristics of the test but also by specimen handling and other laboratory processes.

Biomarker: Following an Institute of Medicine report[d], we define a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a[n] … intervention." Biomarkers can serve many different purposes, including disease classification (e.g., diagnosis and screening), prognosis or prediction, guiding individual treatment choices, use as surrogate outcomes (biomarkers of outcomes), or measuring past toxic or preventive exposures.

Clinical utility: Clinical utility refers to whether a test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to patients and physicians, e.g., in decision making about therapy. Utility is often determined by whether the diagnostic or predictive accuracy of a test can be translated into meaningful clinical outcomes.

Clinical validity: A test's ability to diagnose a disorder, assess susceptibility or risk, or provide information on prognosis or variation in drug response. Clinical validity differs from analytic validity in that it measures the diagnostic or predictive accuracy, rather than technical performance, of a test.

Genetic test: For the purpose of this review we will adopt the definition of a genetic test proposed by the Secretary's Advisory Committee on Genetics, Health, and Society[47]: "A genetic or genomic test involves an analysis of human chromosomes, deoxyribonucleic acid, ribonucleic acid, genes, and/or gene products (e.g., enzymes and other types of proteins), which is predominately used to detect heritable or somatic mutations, genotypes, or phenotypes related to disease and health."

Phenotypic test: A phenotypic test is a means of evaluating the physiological characteristics of a patient. In the context of this review, phenotypic testing specifically refers to testing of platelet reactivity (see below).

Platelet activation: Activation of platelets is a chemical process by which platelets are induced to change shape and aggregate in the blood. *In vivo,* platelet activation occurs

[d] Available at http://www.iom.edu/Reports/2010/Evaluation-of-Biomarkers-and-Surrogate-Endpoints-in-Chronic-Disease.aspx; last accessed September 19, 2011.

when there is a break in the endothelium that exposes circulating inactive platelets to ADP or other molecules that trigger platelet activation.

Platelet reactivity: Platelet reactivity is the degree to which platelets are able to be activated, that is, the extent to which they are responsive to signals in the blood that activate them to clot (see "platelet activation" above). This is of interest because clopidogrel is an antiplatelet drug that is used to decrease the reactivity of platelets (by preventing ADP from binding to them, thereby reducing the risk of clotting). Platelet reactivity is measurable with the use of a variety of laboratory tests. Because platelet reactivity is an intermediate phenotype between exposure to a drug and occurrence of a clinical event (e.g., an arterial thrombotic event), we refer to tests of platelet reactivity as "phenotypic tests" (see above).

Polymorphism: A gene that can occur in more than one form (i.e., consisting of more than one possible DNA sequence for a specific locus); also called a genetic variant. Since humans carry two copies (i.e., alleles) of each gene, a polymorphism can result in the coexistence of more than one encoded protein in a population. Our review focuses on polymorphism of a cytochrome P450 gene, the CYP2C19 gene, which converts clopidogrel into its active form. The gene has more than 35 identified variants (indicated as "*1", "*2", and so on). Some variants encode a protein with normal enzymatic activity (corresponding to normal metabolizing of clopidogrel), other variants encode a loss-of-function protein with no enzymatic activity (corresponding to a nonmetabolizer phenotype), and still other variants lead to increased enzymatic activity (corresponding to an ultrametabolizer phenotype). Combinations of variants at multiple loci add to the possible combinations seen among individuals.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all Evidence-based Practice Center (EPC) reviews, Key Questions are reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to ensure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions will be posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end users, individuals are invited to serve as Key Informants, and those who present with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methods experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They will be selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual Technical Experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind or contribute to the writing of the report and do not have an opportunity to review the report until the public review period.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts, and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Approximately five experts in the field will be asked to peer review the draft report and provide comments. Peer reviewers are invited to provide written comments on the draft report on the basis of their clinical, content, or methodological expertise. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports, such as reports requested by the Office of Medical Applications of Research of the National Institutes of Health, there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in the writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical Briefs, be published three months after the publication of the Evidence Report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

It is our policy not to release the names of the peer reviewers or Technical Expert Panel members until the report is published so that they can maintain their objectivity during the review process.